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Original article

Non-steroidal anti-inflammatory drugs and perforated diverticular disease: a case-control study

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Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide range of side-effects in the gastrointestinal tract and the large intestine. This study examines the hypothesis that the use of NSAIDs is associated with colonic perforation in diverticular disease. Histological evidence was used to confirm perforation. A retrospective review of case records and pathology reports identified 20 patients admitted over 3 consecutive years. A total of 125 age- and sex-matched patients diagnosed with diverticular disease not complicated by perforation formed the control group. The incidences of NSAID use in the two groups were compared. A second control group consisted of 600 age- and sex-matched randomly selected patients with no known diverticular disease admitted as emergencies in the same period. Of the 20 patients with perforation, 9 were taking NSAIDs for 4 weeks or longer, compared with 19 (15%) of the 125 patients who did not have perforation (relative risk 2.961, 95% confidence interval 1.507–5.348, $P < 0.01$). 19% of all patients with diverticular disease were taking NSAIDs compared with 10% of the second control group (relative risk 1.869, 95% confidence interval 1.237–2.781, $P < 0.01$). The findings indicate a strong association between the use of NSAIDs and the perforation of colonic diverticula. The majority of the indications for the use of NSAIDs were cardiovascular and musculoskeletal conditions. Prescribing NSAIDs to patients with diverticular disease carries an increased risk of colonic perforation.

Key words: Non-steroidal anti-inflammatory agents – Diverticulosis – Diverticulitis – Colonic

Non-steroidal anti-inflammatory drugs has a high incidence of damaging side-effects on both normal small and large bowel mucosa. These include ulceration, bleeding, stricture, enteropathy, colitis and perforation.[1] Langman *et al.* found patients with either small or large bowel perforation or haemorrhage were more than twice as likely to be takers of anti-inflammatory drugs.[2] An association between NSAIDs consumption and the complications of diverticular disease, including haemorrhage and perforation, was demonstrated in a prospective study by Wilson *et al.*[3] In another study, Campbell *et al.* found 48% of patients with severe complications of diverticular disease were taking NSAIDs, compared with 20% of patients with uncomplicated diverticular disease.[4] The present study was undertaken to test the hypothesis that there is an association between the use of NSAIDs and perforated diverticular disease. Previous studies did not give a clear definition of perforation and did not assign patients on the basis of histological evidence. This makes the cumulative evidence to date not entirely convincing. By definition, microperforation has occurred in virtually every case of diverticulitis.[5] This is usually walled-off by the pericolic tissues.

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Table 1 Number of patients using NSAIDs

	Perforated diverticular disease	Diverticular disease without perforation	Controls
Users	9	19	62
Non-users	11	106	538
Total	20	125	600

The resultant peridiverticulitis can produce a heavy inflammatory exudate, which often has the appearance of peritonitis. 'Peritonitis' at laparotomy had been the main evidence of perforation in previous studies. In this study, only autopsy confirmation and positive histology were acceptable. Hinchey *et al.* classified perforation as: stage I – contained pericolic abscess or phlegmonous diverticulitis; stage II – walled-off pelvic abscess secondary to perforation of a pericolic abscess; stage III – generalized purulent peritonitis secondary to rupture of a pericolic abscess (also known as perforated diverticulitis; and stage IV – faecal peritonitis (free perforation of a non-inflamed diverticulum).[6] The patients with perforation in this study had stage II, III or IV perforations.

Patients and Methods

All patients with diverticular disease diagnosed between 1995 and 1997 inclusively were identified from the hospital computerized coded information system. The study group consisted of those patients with confirmed perforation. The control group was age- and sex-matched patients with confirmed diverticular disease not complicated by perforation. The case notes were reviewed for each patient. The criteria for the diagnosis of diverticular disease were clinical history (left iliac fossa pain, nausea, diarrhoea) and signs (left iliac fossa tenderness, mild pyrexia, leukocytosis), in addition to positive barium enema, colonoscopy, or macroscopic appearance of the colon at laparotomy or autopsy. The criterion for perforation was the histology of the diseased large bowel segment resected at laparotomy or autopsy. Patients with probable symptoms and signs of diverticular disease but no radiological or endoscopic confirmation were excluded from the study. Patients with what appeared to be peritonitis at laparotomy but confirmed histologically as stage I perforation were not considered to have perforation. Evidence of NSAIDs' use was collected from the clinical history recorded at the time the patient presented. This is correlated with clinical notes from previous admissions under any specialty to verify the timing and duration of use. Patients taking NSAIDs regularly for specific conditions were regarded as users. Those taking the drugs on an 'as required' basis were considered non-users. The name of the NSAID and the clinical indication in each patient was documented. The second control group consisted of 600 randomly selected age- and sex-matched patients admitted as emergencies during the same 3 years. Randomization was by proportionate stratified random sampling based on age strata. None of the patients had known diverticular disease. The incidence of NSAIDs use for each group was then calculated and statistically analysed.

Table 2 Diagnostic evidence of diverticular disease

	Perforated diverticular disease (n = 20)	Diverticular disease without perforation (n = 125)
Barium enema (BE)	1	98
Colonoscopy (COL)	0	56
BE and COL	0	34
Laparotomy	15	5
Autopsy	4	0

Results

A total of 20 patients (10 men, 10 women; median age, 72.5 years) with histologically proven perforated diverticula and 125 age- and sex-matched controls with non-perforated diverticular disease were identified. Of the total of 145 patients, 74 (51%) were admitted as emergencies, and 71 (49%) had subacute symptoms seen as out-patients. Seven patients, histologically shown to have less than stage II perforations, were excluded from the study group. Nine of the 20 patients in the study group were taking a non-steroidal anti-inflammatory drug for at least 4 weeks (range, 4 weeks to 9 years), compared with 19 (15.2%) of the 125 patients with no perforation (Table 1). The ccc^2 value with Yates' continuity correction was 8.00698, P = 0.0017. The odds ratio for the incidence of NSAIDs use was 4.565 (CI, 1.667, 12.498), with a relative risk of 2.961 (CI, 1.507, 5.348). The use of NSAIDs in all 145 patients as a group compared with the 600 controls had an odds ratio of 2.077 (CI, 1.273, 3.386) and relative risk of 1.869 (CI, 1.237, 2.731); ccc^2 = 8.0354, P = 0.0029. Fisher's exact probability tests also obtained significant results with similar confidence intervals.

Of the 20 patients with perforation, diverticular disease was first diagnosed at laparotomy in 15, and at autopsy in 4 (Table 2). Two of the patients who had autopsy had faecal peritonitis and 2 had purulent peritonitis; they died before operation. All of the other 16 patients underwent laparatomy and Hartmann's procedure. Three died post-operation (range, day 1 to day 19). One of the 20 patients had a perforated diverticulum of the ascending colon, the rest had sigmoid perforations. Of the 16 patients who underwent operation, 3 were stage II, 12 were stage III, and 1 was stage IV perforation. The 7 excluded patients who underwent laparotomy had severe perisigmoiditis (3 patients), phlegmonous diverticulitis

Table 3 Name of NSAID and the number of users

NSAID	Perforated diverticular disease	Diverticular disease without perforation	Controls
Aspirin	6	17	38
Diclofenac	1	0	11
Ibuprofen	1	1	8
Naproxen	0	1	2
Indomethacin	0	0	3
Piroxicam	1	0	0
Total	9	19	62

Table 4 The clinical indications for which patients were taking NSAIDs

Disease	Perforated diverticular disease	Diverticular disease without perforation	Controls
Cardiovascular	5	8	27
Osteo-arthritis	2	7	22
Cerebrovascular	1	4	6
Gout	1	0	3
Rheumatism	0	0	2
Back pain	0	0	2

(2 patients), colo-enteric fistula and diverticular adhesion to the ovary, respectively.

Each of the NSAIDs taken by patients was prescribed. Among the 9 patients on NSAIDs in the perforation group, 6 were taking aspirin (Table 3). The users in the two control groups were taking similar NSAIDs with the addition of indomethacin and naproxen. Aspirin is the most frequent NSAID in all three groups. The dose of each drug individual patients were using was mainly standard, *e.g.* 75 mg o.d. for aspirin, 400 mg t.d.s. for ibrufen. The medical conditions for which the patients were using NSAIDs fell into the major categories of musculoskeletal, rheumatological, cardiovascular and cerebrovascular diseases (Table 4). Osteo-arthritis of the hip and knee joints contributed to the majority of the musculoskeletal group. The cardiovascular group consisted of ischaemic heart disease, atrial fibrillation, hypertension and peripheral vascular disease. Patients in the cerebrovascular group had a history of transient ischaemic attacks or cerebrovascular accidents. In the group with perforation, 2 patients with osteo-arthritis, and 1 patient with ischaemic heart disease and gastric ulceration were not taking NSAIDs.

Discussion

This study was motivated by the persistent high morbidity and mortality rates in patients with complicated diverticular disease both in our region and nation-wide.[7,8] In the 5-year audit by Elliot *et al.*, all deaths occurred in patients who required operation for bowel obstruction, or septic complications secondary to perforation. For the survivors, the reversal of a Hartmann's operation at a later stage carries substantial morbidity and mortality.[9]

In this case-control comparison, patients who had serious perforations were nearly 3 times more likely to be takers of NSAIDs than patients with uncomplicated diverticulosis or diverticulitis. Steroids have also been shown to be a risk factor for perforation in diverticular disease.[10] In some of the previous studies, a considerable number of the patients taking NSAIDs were also taking steroids although after excluding these, the association between NSAIDs and perforation was still statistically significant.[2,3] Our study was not confounded in this manner as none of the patients was on steroids. In addition, there are four observations. Firstly, the majority of patients who had perforation did not have previously documented symptoms of diverticular disease. This suggests that clinical severity or past history does not predict the effects of NSAIDs on diverticular disease. It appears that NSAIDs can predispose even asymptomatic disease to serious complications. Secondly, aspirin is the most common drug implicated in perforation. Thirdly, while arthritic conditions were the main indications for the use of NSAIDs by patients in other series, cardiovascular conditions predominate in this study, including among the control subjects. This explains why aspirin is the most frequently used NSAID in our series, since the other NSAIDs are not primarily used in cardiovascular diseases. Fourthly, none of the patients was using NSAIDs to alleviate the symptoms of diverticular disease. Therefore, the observed differences in the incidence of NSAID's use are not secondary to the presence of the disease itself.

The retrospective design of the study has its inherent weakness. It is dependent on the accuracy of the case histories recorded by various doctors at the time of presentation. It also presumes that patients on NSAIDs take their medications regularly. However, it has the advantage of including those patients with asymptomatic or largely asymptomatic diverticulosis who later developed perforation. These patients have not consulted their medical practitioners and have not had investigations. Therefore, this study is not biased by the assumption that NSAIDs have no effects on minimal or mild diverticular disease.

It is not certain how NSAIDs predispose colonic diverticula to perforation. The pathophysiology is likely multifactorial. Whether there is a temporal relationship or a dose-related effect awaits elucidation. The central mechanism appears to be the inhibition of the enzyme cyclo-oxygenase resulting in deficient levels of prostaglandins.[11] Two isoenzymes exist: cyclo-oxygenase 1 (COX-1), which

makes physiological prostaglandins involved in the protection of bowel mucosa, and cyclo-oxygenase 2 (COX-2), which is pro-inflammatory.[12] It is probable that inhibition of COX-1 by NSAIDs reduces the amount of mucosal prostaglandins in diverticula predisposing them to perforation. However, COX-2 inhibition is anti-inflammatory and may lead to the failure of the immune response to localize a microperforation. The preferential inhibition of COX-2 by the newer NSAIDs, such as meloxicam, has reduced gastrointestinal adverse events.[13] Whether this approach is applicable to diverticular disease remains to be seen. In an animal study by Reuter *et al.*, inflamed colon perforated when selective COX-2 inhibitors were administered for a week.[14] The possible link between the action of NSAIDs on the inflammatory response and diverticular perforation is supported by. evidence that immunosuppression contributes to perforation. Patients on immunosuppressives after organ transplantation, patients taking high-dose, or long-term steroids and patients with the acquired immune deficiency syndrome have an increased risk of perforated diverticular disease.[15–17] The local effects of NSAIDs on the large bowel mucosa may also be important. For example, acute perforation has occurred in association with slow-release indomethacin.[18]

NSAIDs are commonly used drugs for common medical conditions. The number of prescriptions has been rising in recent years.[19] Many are available without prescription and are common ingredients of mixtures sold over the counter. By measuring platelet cyclo-oxygenase activity in patients, a study has shown that there are more aspirin users than clinical history alone.[20] At the same time, diverticular disease has a high prevalence in the general population. About 5–10% of those aged more than 45 years are likely to have diverticulosis, rising to 80% among those aged more than 85 years.[21]. Given the frequency of painful conditions and cardiovascular diseases in the general population, the coincidence of NSAID use and the presence of diverticular disease would not be an uncommon event.

Conclusions

This study has re-inforced the growing body of evidence that NSAIDs are associated with perforated diverticular disease. Many benefits from the analgesic, anti-inflammatory, anti-pyretic and antithrombogenic actions of NSAIDs have been gained with a concurrent risk of life-threatening septic complications. How to balance this risk-benefit ratio for individual patients, what is the profile of the high-risk patient, and many other unanswered questions demand larger clinical studies. Experimental models are needed to investigate the pathological effects of NSAIDs on the colonic diverticulum. This study has further emphasized the rule that NSAIDs should always be prescribed with a considerable amount of caution. Clinicians assessing any ill patient with an acute abdomen should consider the possibility of perforated diverticular disease, especially when the patient is on NSAIDs.

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